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(54) Title: PROCESS FOR THE PREPARATION OF PHARMACEUTICAL MICROCAPSULES WITH ENHANCED TASTE-MASKING AND HIGH DISSOLUTION RATE

(57) Abstract: Process for the production of microcapsules containing a drug and comprising a layer of ethylcellulose and a layer of an acrylic polymer and microcapsules produced thereby.

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PROCESS FOR THE PREPARATION OF PHARMACEUTICAL MICROCAPSULES WITH ENHANCED TASTE-MASKING AND HIGH DISSOLUTION RATE

Field of the invention

The present invention relates to the field of microencapsulation of active principles.

A new process is described allowing to obtain pharmaceutical microcapsules with enhanced taste masking and an optimal dissolution profile.

State of the art

Achieving an effective encapsulation of active principles is important for the preparation of a variety of compositions; when microparticles of an active principle must be singly provided with an external coating, microencapsulation techniques are employed.

The microencapsulation process consists in coating small drug cores (microparticles) with a layer of polymer. The polymer layering may be achieved by different techniques; in particular the microencapsulation by phase separation (or coacervation), proved very reliable in obtaining coated microparticles (M.Calanchi, "Taste Masking of oral formulations", *Pharmaceutical Manufacturing International*, pp.139-141, 1996; L. Dobetti, S. De Luigi, "Developments in Microencapsulation", *Pharmaceutical Manufacturing and Packaging Sourcer,* p. 39-40, Dec.1988).

The production of microcapsules differs from normal drug coating techniques in that singly coated, discrete microparticles must be obtained, e.g. in the order of 500 μm or less: to achieve this goal, the aggregation of the formed microcapsules must be avoided.

In the pharmaceutical field, microencapsulation of active principles is applied in particular to prepare pharmaceutical multiparticulate compositions such as syrups, permanent or temporary suspensions, chewable or fast melting tablets, etc.. The microencapsulation is used in particular to mask the taste of those drugs characterised by bitterness, throat-burning, saltiness and localised numbing of the tongue, etc.

Microencapsulation is also used to modulate the drug release profile after administration. In principle, both taste masking and release-controlling properties are obtained by increasing the thickness of the microcapsule wall. As a

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consequence, it is easy to prepare taste-masked, slow-release microcapsules, whereas it is more difficult to obtain taste-masked quick-release ones: the latter form is nevertheless very desired, in particular for those drugs with unpleasant taste which, for pharmacokinetic and pharmacodynamic reasons, must be delivered quickly in the stomach: one typical example is that of antibiotic drugs (for example Penicillins, Cephalosporins, Carbapenem, Penems, Penams, Aminoglycosides, Macrolides, Ketolides, Tetracyclines, Quinolones, etc.) which are often endowed with an unacceptable taste: they require a strong taste-masking, but at the same time they must be delivered and absorbed quickly in the stomach, so to ensure a quick onset of action and avoid disturbing the intestinal bacterial flora.

A second example is that of antinflammatory drugs or drugs for pain relief. Often this kind of drugs needs to be taste masked to avoid bitterness or throat burning, but at the same time a fast absorption is mandatory to assure a fast pain relief.

Third example is that of drugs characterised by a narrow absorption window. These drugs require a fast release in the first part of the gastrointestinal tract to guarantee the proper bioavailability.

For the purpose of obtaining a good taste masking, the preferred and most widely used sealing polymer is ethylcellulose. This polymer is characterised by an efficient sealing capacity and is easily layered onto the drug microparticles; in addition it is an absolutely safe excipient, free from toxicity problems. However ethylcellulose-coated microparticles are not capable to associate, to the good taste masking, an elevated dissolution rate in the stomach. In order to overcome this problem, attempts have been made to reduce the thickness of the microcapsule wall (i.e. using less encapsulating polymer); however this is not a good solution because the taste-masking is no longer ensured by the thinner coating. The use of coating polymers alternative to ethylcellulose, having e.g. higher solubility in the stomach is equally unsatisfactory : in fact, these polymers require much a thicker coating to achieve the same level of taste masking of ethylcellulose; as a result microcapsules with very low potency are obtained: they require bulky dosage forms such as large tablets or capsules, thus quite problematic from the point of view of patient acceptability. In addition, with respect to ethylcellulose, polymers

with higher solubility present problems of particle aggregation during the coating process, with the result that small-size singly coated microparticles are yet more difficult to obtain.

At present no microencapsulation process is available, capable to produce small microcapsules, ensuring at the same time a good taste masking, a fast onset of action, and a high potency.

Summary of the invention

The present application discloses a microencapsulation process characterised by coating drug cores with a first layer of ethylcellulose and further coating the obtained microcapsules with a layer of an acrylic polymer. The obtained microcapsules show a high potency, an optimal taste masking, and ensure a quick release in the stomach. The invention allows thus to produce superior pharmaceutical formulations, especially useful in the case of drugs with unpleasant taste in particular drugs, which require an immediate delivery in the stomach, even if the administration in form of reconstitutable suspensions is required.

Description of the figures

Figure 1: Caffeine, microscope image of lot. B1, described in the experimental part, showing an evident aggregation phenomena.

Figure 2: Teophylline, particle size distribution of microcapsules of invention (lot. C2)

Figure 3: Fluoxetine, microscope image of lot. C3, representing the microcapsules of the invention.

Figure 4: Caffeine, microscope image of lot. C1, representing the microcapsules of the invention.

Detailed description of the invention

A first objective of the present invention is a process for the production of microcapsules containing a drug, characterised by the following steps:

a. - coating drug microparticles with a layer of ethylcellulose

b. - further coating the product of a. with a layer of an acrylic polymer

The present process is particularly suitable for those drugs which have an unpleasant taste and require quick delivery into the stomach; however, any drug

available in microparticular form can be subjected to the present process; for the purpose of the invention, the term "drug" includes also mixtures of two or more of them.

The step a. obtains singly coated microcapsules. The coating step a. can be performed by microencapsulation techniques which, as such, are well-known in the art. Among them, microencapsulation by phase separation (also known as microencapsulation by coacervation) is preferred.

The known process of phase separation can be summarised in the following, non limitative, step sequence: (i) *dispersion*: the creation of a two phase system in which a liquid phase (e.g. ethylcellulose solution in cyclohexane) and a solid phase (drug particles) are present simultaneously; (ii) *phase separation*: thanks to the action of the coacervation-inducing agent (e.g. an ethylene polymer like epolene) a third phase is formed. This phase called *coacervate* is a highly concentrated polymer solution in solvent which spreads onto the surface of the suspended drug cores. As a result, fluid droplets of coacervate coalesce and enwrap the drug cores with a continuous layer of membrane (*gel phase*). The deposition of the polymeric membrane is promoted by a reduction of the total free interfacial energy brought about by the decrease of the coating material surface area during the coalescence of the liquid droplets; (iii) *hardening*: the fluid polymeric film is hardened by cooling down the suspension to room temperature; (iv) *separation*: microcapsules are separated from the liquid medium by settling. The supernatant is then removed and the microcapsules can be washed with fresh solvent to remove the residues of phase separation agent. Finally the microcapsules are filtered, dried and sifted.

Another known technique applicable to perform step a. is the fluidized bed coating. In this case the ethylcellulose coating can be ensured by spraying onto pharmaceutical cores either an organic solution or an aqueous dispersion of the polymer. The choice is strictly dependent on the chemical and physical characteristics of the cores to be coated.

If the next step b. is also performed by fluidized bed coating, the overall process is particularly advantageous in that it can be performed in the same reactor by simply changing the coating solution when passing from step a. to b.

The product of step a. is an ethylcellulose microcapsule containing the drug. Preferably the obtained microcapsule has a drug / ethylcellulose weight ratio comprised between 1:1 and 30:1, more preferably between 3:1 and 15:1. The drug / ethylcellulose weight ratio is herein referred as PR (phase ratio).

To apply the additional coating of acrylic polymer (step b.), it is preferable to use a spray-coating technique: according to this embodiment, the microcapsules obtained in step a. are suspended in a fluidised bed and sprayed with a solution or suspension of the acrylic polymer. Preferably, the solvent used to form this solution or suspension is an acidic aqueous solvent, a hydroalcoholic solvent, an organic solvent, or mixtures thereof. When a hydroalcoholic solution is used, it preferably comprises the following weight percentages of components, calculated with respect to the total weight of the solution:

acrylic polymer: 4-20%, preferably 7-20%

alcohol (e.g. ethanol): 30-94%, preferably 40-75

water: 0-40%, preferably 10-35%

micronised inorganic material (e.g. talc): 2-20%, preferably 5-9%.

The acrylic polymer can be layered indifferently during one or more layering steps: in the latter case a multilayered acrylic coating is obtained.

Advantageously, the product of step b. has an acrylic polymer content comprised between 5% and 40% by weight ; an optimal range of this polymer is 10-25%

The acrylic polymer used in step b. is chosen among acrylic polymers for pharmaceutical use: they are well-known in pharmaceutical technology, and can be indifferently linear, branched and/or cross-linked polymers of acrylic and/or methacrylic acid.; the chosen polymer must be soluble at acidic pH, (e.g. 1 g dissolves in 1N HCl); Representative, but not limitative examples of these polymers are the products of the class comprising Eudragit E (cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters).

A further object of the present invention are the microcapsules obtained by the process above described. The process according to the present invention allows to obtain small taste-masked microcapsules (i.e. having a weight median diameter comprised between 20 – 800 μm, preferably 100 - 400 μm, with potency (i.e. mg drug/g of the end product of step b.) comprised between 400 and 950 mg/g, and

capable to release at least 80% of the drug contained therein within 30 minutes, preferably in 10 minutes in a simulated gastric fluid test or in acidic media. The high level of potency is a pharmaceutically advantageous feature which allows to obtain, at constancy of drug content, smaller tablets or capsules, (i.e. containing lesser amounts of coating polymers) which are being more acceptable by the patient. The reduction in the amounts of coating polymers involves the further advantage that the present compositions can dissolve in water without forming thickened viscous solutions around the drug cores: this further eases the drug diffusion and the establishing of a fast onset of action. The obtained microcapsules further show the advantage of an improved suspendability in water, i.e. they do not form aggregates, do not float on the surface of a suspending medium, nor they adhere to side walls of a glass: therefore they do not require a separated wetting treatment with surfactants, such as instead required in case of ethylcellulose microcapsules.

Moreover the obtained microcapsules show the capability of maintaining the taste masking properties when suspended in neutral or basic aqueous media. The use of resuspended dosage form is often required for easiness and effectiveness of administration (e.g. dosage form as monodose sachet and dry powders for extemporaneous suspension).

The above described microcapsules, simultaneously ensuring elevated taste masking / elevated potency / elevated dissolution rate, are new and represent a further object of the present invention. These microcapsules can be further processed, optionally in presence of suitable pharmaceutical excipients, into suitable pharmaceutical formulations, e.g. dry powders for extemporaneous suspensions, tablets, minitablets, microcapsule-containing capsules, monodose sachets, fast disintegrating tablets, syrups, etc.

The process and microcapsules of the invention can be used to taste-mask a wide variety of active ingredients that have a bitter or non-bitter taste and that are desired to be released rapidly. Active ingredients useful with this invention include antibiotic and antibacterial agents such as ketolides; antiviral agents, analgesics, anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-

inflammatory agents, antiemetics, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, H2 antagonists, cardiovascular drugs, antiarrhythmics, antihypertensives, ACE inhibitors, diuretics, vasodilators, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, psychostimulants, sedatives, antimigrane agents antituberculosis agents and tranquilizers. Generally, the actives used in conjunction with the present methodology are those which are bitter or otherwise unpleasant-tasting and thus in need of taste masking.

The present invention is now illustrated by reference to the following experimental examples which have no limiting function.

EXPERIMENTAL PART

Equipment

- 5 L microencapsulation reactor
- pneumatic stirrer/ propeller
- break-water
- thermostat
- Tray dryer
- Fluid bed

Materials

- Caffeine
- Teophyilline
- Fluoxetine
- Ethylcellulose
- Polyethylene
- Cyclohexane
- Eudragit E
- Micronised talc
- Ethanol
- Purified water

Process description

Phase separation

3000 g of cyclohexane were poured into a 5L jacketed stainless steel reactor.

Then, under a gentle stirring ensured by a helix, a fixed amount of drug, ethylcellulose and polyethylene were added.

The stirring rate was then increased to 500 rpm. The system was then heated to 80°C to cause the ethylcellulose solubilisation in cyclohexane.

The final microcapsules were dried in an oven overnight at 40°C and sifted by 500 µm screen.

Fluid bed coating

A fixed amount microcapsules obtained as described in the previous paragraph were loaded in a Glatt GPCG 1 fluid-bed equipped with 4" Wurster insert, plate type B, spraying nozzle 1.0 mm, and sprayed with a coating suspension having the following qualitative composition:

Eudragit® E100

Micronised talc

Ethanol

Purified water

The second layer of coating suspension were subsequently applied. The final product was sifted by 500 µm screen. The coating level obtained was calculated as microcapsules theoretical weight gain.

Residual cyclohexane, residual ethanol and residual polyethylene were well within the acceptance limits for pharmaceuticals.

Analytical methods

Dissolution Rate *Method (i):*

USP Paddle, 900 mL or 500 mL, HCl 0.1N or pH 1.2 buffer, 50 or 100 rpm, 37 °C

Samples were collected at fixed times, during, at least, 30 minutes time period.

Data at 10 minutes and 30 minutes are reported.

Taste Masking evaluation (TM)

Obtained by sensorial judgement.

A fixed amount of microcapsules was evaluated as is or after suspension in a appropriate aqueous media.

Particle Size Distribution (PSD)

Performed by sieve analysis using the automatic siever mod. Octagon Digital, equipped with sieves (Endecotts types).

D. Optical Microscopy (PSD)

Performed by a Ortolux microscope and a Zeiss Axioscopic 2 microscope.

EXPERIMENTAL RATIONALE

Three experimental sets were performed.

In the first set only the coating (i.e. ethylcellulose) was applied.

In the second set only the layer of the acrylic polymer was applied.

In the third set the drug microparticles were first coated with a layer of ethylcellulose and further with a layer of an acrylic polymer, according to what described in the present invention.

RESULTS

First Set

Drug	Coating % w/w	TM	DRT 10 min	DRT 30 min	PSD	Potency % w/w	Batch
Caffeine	10	--	> 80 %	> 80 %	++	90	A1
Caffeine	30	++	30 %	54 %	++	70	A2
Theophylline	10	--	> 80 %	> 80 %	++	90	A3
Theophylline	15	--	57 %	> 80 %	++	85	A4
Theophylline	35	++	19 %	44 %	++	65	A5
Fluoxetine	15	--	> 80 %	> 80 %	++	85	A6
Fluoxetine	20	--	> 80 %	> 80 %	++	80	A7
Fluoxetine	30	+-	37 %	65 %	++	70	A8

Legenda:

PSD (Particle Size Distribution)

++ : No significant aggregation

--: Significant aggregation

+- : Improved but not acceptable

TM (Taste Masking)

++ : Satisfactory

-- : Not satisfactory

+- : Improved but not acceptable

From the evaluation of the aforementioned results, it's evident that:

- at low level of coating the dissolution rate is quite fast, but the taste masking is not acceptable
- at higher level of coating the taste masking properties significantly improve, but the release profile is too slow and therefore not acceptable. Moreover the potency decreases dramatically
- in some cases, even using higher levels of coating (with a significant decrease of the dissolution rate), the taste masking is not acceptable. This is probably related to a higher surface area of the drug used.
- the application of ethylcellulose, even at high percentage, leads to acceptable particle size distribution

Second Set

Drug	Coating % w/w	TM	DRT 10 min	DRT 30 min	PSD	Potency % w/w	Batch
Caffeine	10	--	n.a.	n.a.	--	90	B1
Theophylline	25	--	> 80%	> 80%	+-	75	B2
Theophylline	40	--	> 80%	> 80%	+-	60	B3
Fluoxetine	30	--	> 80%	> 80%	--	70	B4
Fluoxetine	40	--	> 80%	> 80%	--	60	B5

n.a.: not available. DRT was not performed due to dramatic agglomeration phenomena

Legenda:

PSD (Particle Size Distribution)

++ : No significant aggregation

--: Significant aggregation

+- : Improved but not acceptable

TM (Taste Masking)

++ : Satisfactory

-- : Not satisfactory

+- : Improved but not acceptable

From the evaluation of the aforementioned results, it's evident that:

- the application of the acrylic polymer, even at high percentage, doesn't affect significantly the release in simulated gastric fluid, but is not able to assure the required taste masking
- even applying a low level of acrylic polymer, the particle size distribution resulted not acceptable due to agglomeration phenomena.

In order to overcome this drawback, the coating of batches B2 and B3 was performed using a very low spraying rate, leading to a time consuming process, not economically compatible with an industrial application of this technology.

Despite using this condition, the particle size distribution was not considered completely satisfactory due to a residual aggregation. Anyway the taste masking properties were not satisfactory.

Third Set

Drug	I Coating % w/w	II Coating % w/w	TM	DRT 10 min	DRT 30 min	PSD	Potency % w/w	Batch
Caffeine	7.5	25	++	>80 %	>80 %	++	67.5	C1
Theophylline	11.3	25	++	54 %	>80 %	++	63.7	C2
Fluoxetine	24.2	15	++	76 %	>80 %	++	60.8	C3

Legenda:

PSD (Particle Size Distribution)

++ : No significant aggregation

–: Significant aggregation

+- : Improved but not acceptable

TM (Taste Masking)

++ : Satisfactory

– : Not satisfactory

+- : Improved but not acceptable

From the evaluation of the aforementioned results, it's evident that:

- The application of the two layers leads to microcapsules able to properly mask the taste, even when suspended in a liquid media, and also ensuring a fast

release and avoiding significant microcapsule aggregation.

- Moreover the overall coating amount is relatively low, so ensuring the possibility to obtain suitable potency.

CLAIMS

1. A process for the production of microcapsules containing a drug, characterised by the following steps:

a. coating drug microparticles with a layer of ethylcellulose

b. further coating the product of a. with a layer of an acrylic polymer

2. A process according to claim 1, where the coating in step a. is applied by phase separation microencapsulation or by fluidized bed coating.

3. A process according to claims 1-2, where the coating in step b. is applied by spraying a solution or suspension of acrylic polymer onto the particles obtained in a., suspended in a fluidised bed.

4. A process according to claim 3, where said solution or suspension is a hydroalcoholic solution, comprising the following weight percentages of components, calculated with respect to the total weight of the solution:

- acrylic polymer: 4-20%
- alcohol: 30-94%
- water: 0-40%
- micronised inorganic material: 2-20%

5. A process according to claim 3, where said hydroalcoholic solution or suspension comprises the following weight percentages of components, calculated with respect to the total weight of the solution:

- acrylic polymer: 7-20%
- alcohol: 40-75%
- water: 10-35%
- micronised inorganic material: 5-9%

6. A process according to claims 4-5, where said alcohol is ethanol, and said inorganic material is talc.

7. A process according to claims 1-6, where the product of step a. has a drug / ethylcellulose weight ratio (phase ratio) comprised between 1:1 and 30:1, and the product of step b. has an acrylic polymer content comprised between 5% and 40% by weight .

8. A process according to claim 1-6, where the product of step a. has a drug / ethylcellulose weight ratio (phase ratio) comprised between 3:1 and 15:1, and the

product of step b. has an acrylic polymer content comprised between 10% and 25% by weight.

9. A process according to claims 1-8, where the taste-masked microcapsules obtained in step b. have a weight median diameter comprised between 20 and 800 µm, preferably 100 - 400 µM, drug potency comprised between 400 and 950 mg/g, and are capable of releasing at least 80% of the drug contained therein within 30 minutes preferably within 10 minutes in a aqueous acidic media.

10. Microcapsules containing a drug, obtainable by the process described in claims 1-9.

11. Microcapsules according to claim 10, formulated in a pharmaceutical administrable form.

12. Microcapsules according to claim 11, wherein said pharmaceutical administrable form is chosen from dry powders for extemporaneous suspensions, tablets, minitablets, microcapsule-containing capsules, monodose sachets, fast disintegrating tablets, syrups.

13. Microcapsules according to claims 10-12, wherein said drug is chosen from penicillins, cephalosporins, carbapenem, penems, penams, aminoglycosides, macrolides, ketolides, tetracyclines, quinolones.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, FSTA, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 52848 A (EURAND AMERICA INC) 26 July 2001 (2001-07-26) abstract page 4, line 7-11 claims 1,5-8	1-13
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X	WO 00 30617 A (CIMA LABS INC) 2 June 2000 (2000-06-02) examples 1-4	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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